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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/497,943	02/04/2000	Mark Aaron Behlke		8098

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/497,943	BEHLKE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33,35-41,43-48 and 55-57* is/are pending in the application.

4a) Of the above claim(s) *1-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-33,35-38,40,41,43-46,48 and 55-57* is/are rejected.

7)☒ Claim(s) *39 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01 March 2004 has been entered.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference. In particular, the specification states at page 39: "Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties." Such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971)

> (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 55 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 55 and 56 recite the limitation "the Probe" in line 1. There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 29-33, 35-38, 40, 41, 43-46, 48, and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,882,856 (Shuber) in view of US Patent 5,710,028 (Eyal et al.).

10. For convenience, claim 29, the sole independent claim currently under consideration, is reproduced below.

29. (Currently Amended) A method of labeling an oligonucleotide ~~a nucleic acid molecule,~~ comprising the steps of:

a. hybridizing a first oligonucleotide ~~nucleic acid~~ to a second oligonucleotide ~~nucleic acid~~, wherein the first oligonucleotide ~~nucleic acid~~ comprises, from 3' to 5': a Substrate Hybridization Domain adjoining ~~and~~ a Signal Template Domain, wherein:

i. the Substrate Hybridization Domain consists of a sequence of about 5 to about ~~less than~~ 10 nucleotides; and

ii. the Signal Template Domain consists of ~~comprises~~ a sequence of about 5 to about 100 nucleotides;

and the second oligonucleotide ~~nucleic acid~~ comprises, from 3' to 5': a Template Hybridization Domain adjoining ~~and~~ a Target Binding Domain, wherein:

i. the Template Hybridization Domain consists of a sequence of about 5 to about ~~less than~~ 10 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first oligonucleotide ~~nucleic acid;~~

ii. the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

and:

b. extending the second oligonucleotide ~~nucleic acid~~ with a DNA polymerase in the presence of a labeled nucleotides to create an oligonucleotide having from 5' to 3' an unlabeled Target Binding Domain adjoining~~[[,]]~~ a Template Hybridization Domain adjoining~~[[, and]]~~ a labeled Signal Domain~~, having a complimentary sequence which shows complementarity toward and is hybridizable to the Signal Template Domain.~~

11. It is noted with particularity that while applicant has amended the claim so to recite that one is to hybridize a first "oligonucleotide" to a second "oligonucleotide," there is no absolute limit to the size of the size of the compounds identified as an "oligonucleotides."

12. It is further noted that while the claims now recite that a first and second oligonucleotide "comprises" a first and second domain and that the two domains are "adjoined," the manner or directness of the two domains being adjoined has, for purposes of examination been interpreted as encompassing domains that are directly as well as indirectly adjoined. Accordingly, the various domains of the respective oligonucleotide have been interpreted as being capable of being flanked and separated by additional nucleotides, and that the number of additional nucleotides is virtually without limit so long as the overall length of the oligonucleotide is supported by what is considered in the art to constitute an "oligonucleotide."

13. In view of the recited oligonucleotides being "comprised of at least the recited domains, and fairly encompass the presence of additional sequences, the additional sequences that could be present are by default either complementary or non-complementary to a target sequence, and/or to portions of the "oligonucleotide." Accordingly, these additional sequences may have the same or different properties as that exhibited by the domains positively recited in the claims. *Ex parte Gottzein et al.* 168 USPQ 176 (PTO Bd. App. 1969).

14. Shuber, column 2, third paragraph, and column 4, third paragraph, discloses the use of a chimeric primer that is described as being configured 5'-XY-3'. The "X" domain "comprises a sequence that does not hybridize to the target sequence." The "Y" domain "comprises a sequence contained within or flanking the target sequence or its complement." Accordingly, the "X" domain meets the limitations of applicants "Signal Template Domain" and the "Y" domain

meets the limitations of the "Substrate hybridization Domain" of the "first sequence." The target sequence meets the limitations of applicant's second sequence.

15. As seen at column 4, the respective domains may be comprised of nearly any nucleotide sequence and that it can range in length from 17 to 25 bases. As stated above, the first and second nucleic acids of the claimed method have been interpreted as encompassing any number of nucleotides, and that nucleotides beyond the limits recited for the various domains can be immediately adjacent to the nucleotides that make up said domains, and can have the same property as those nucleotides that comprise said domains. Accordingly, the disclosure of first and second oligonucleotides in the prior art that have an overall length greater than the recited domains is still considered to meet the limitation of the first and second oligonucleotides that are used in the claimed method.

16. Shuber does not teach using RNA as a source material or the use of primers that comprise RNA. Additionally, Shuber et al., do not teach using labeled nucleotides and detecting their incorporation.

17. Eyal et al., column 3, teach explicitly of incorporating detectably-labeled nucleotides at the terminus of a primer so to label a nucleic acid molecule as well as to detect a target nucleic acid in a sample. As seen herein, the detectable label can be radioactive or fluorescent.

18. Eyal et al., column 4, teach that their method is "simple, rapid and highly accurate."

19. Eyal et al., column 1, states that the starting material (at least one of applicant's "nucleic acids") is RNA. Column 9, first paragraph, teaches explicitly of the wide variety of detectably-labeled nucleotides that can be added to the terminus of a second nucleic acid. As seen therein, such nucleotides include ribonucleotides.

20. Neither Shuber nor Eyal et al., disclose the precise ratio or percentage of homopolymeric nucleotides present or the specific activity of the probes used, however, such limitations are considered to be the result of routine optimization and do not constitute a point of novelty. Attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

21. In view of the explicit teachings of benefit (simple, rapid, highly accurate and widely applicable) as taught by Eyal et al., at column 4, one of ordinary skill in the art at the time the invention was made would have been motivated to have modified the method of Shuber such that the time consuming and laborious process of detecting primer extension products on a gel would be avoided by incorporating a detectable nucleotide at the terminus and then detect its incorporation and in so doing not only label a nucleic acid but to also detect a target nucleic acid

of interest. Accordingly, and in the absence of convincing evidence to the contrary, claims 29-33, 35-38, 40, 41, 43-46, 48, and 55-56 are rejected under 35 U.S.C. 103(a).

22. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber and Eyal et al., as applied to claims 29-33, 35-38, 40, 41, 43-46, 48, and 55-56 above, and further in view of US Patent 5,599,708 (Mundy et al.) and US Patent 5,614,389 (Auerbach).

23. See above for the basis of the rejection as it relates to the disclosures of Shuber and Eyal et al.

24. Neither Shuber nor Eyal et al., disclose using a nucleic acid that comprises a hairpin loop.

25. Mundy et al., column 8, teaches performing multiple cycles of primer extension reactions, including reactions using mRNA templates that have a hairpin loop. As noted therein, the mRNA has a loop at its 3' terminus, yet the product of the primer extension reaction can be used in subsequent rounds of amplification. In such second rounds, the hairpin loop would occur at the 5' terminus (a limitation of claim 57).

26. Auerbach, Figure 3A, discloses applicant's first nucleic acid having a hairpin loop region that is 5' to the Signal Template Domain. It is noted that X and X' form the double stranded stem region when the nucleic acid exists in single-stranded form (see Figure 5).

27. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have substituted the first nucleic acid used in the primer extension reaction of Shuber with a nucleic acid that comprises are region known to contain a hairpin loop as Mundy et al., and Auerbach teaches explicitly of annealing a second nucleic acid to just such a first nucleic acid such that primer extension reaction can be conducted.

28. In view of the detailed guidance, the broad applicability and motivation found in the art (Eyal et al.) the ordinary artisan would have been amply motivated to have labeled nucleic acids in such a manner and to have done so with a most reasonable expectation of success. Therefore, and in the absence of convincing evidence to the contrary, claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber and Eyal et al., as applied to claims 29-33, 35-38, 40, 41, 43-46, 48, and 55-56 above, and further in view of US Patent 5,599,708 (Mundy et al.) and US Patent 5,614,389 (Auerbach).

Response to argument

29. At pages 15-16 of the response of 01 March 2004 applicant asserts that the amendments to the claims have overcome the rejection of the claims under 35 USC 103(a), noting with particularity that claim now requires "two oligonucleotides that hybridize to each other" (emphasis in the original).

30. This argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. While agreement is reached in that there needs to be some degree of complementarity, the threshold is minimal. Claim 29 places no minimum limit on the number of nucleotides that need to be complementary, and as such, claim 29 has been interpreted as requiring but a single nucleotide to be complementary between the Template Hybridization Domain and the Substrate Hybridization Domain.

31. Applicant asserts that a point of distinction between the now amended claims and the teachings of Shuber allegedly lies in he absence of a "second oligonucleotide" as not positively recited in claim 29.

32. This argument ahs been fully considered and has not been found persuasive as the limitation of a "second oligonucleotide" is met by the presence of the template. While applicant has defined the regions of the first oligonucleotide (Shuber's template), it is noted with particularity that claim 29 defines the first oligonucleotide as "comprising" a first and second domain. Accordingly, the first oligonucleotide (Shuber's template) can be of virtually any length. It is further noted that the term "oligonucleotide is recognized in the art as comprising nucleic acids of many hundred bases in length. In support f this position, attention is directed to paragraph 84 of US Patent Application Publication 2004/0121377 A1, which teaches:

> otides and modified lipids. The length of the oligonucleotide can range from a single base to many tens or hundreds of bases. Synthetic oligonucleotides are prepared by machine synthesis; much longer sequences can be be added by enzymatic ligation using methods well-known in the recombinant DNA field. Typical examples of linkages include

In view of the breadth accorded by what an "oligonucleotide' may "comprise," the template used in the amplification reaction of Shuber fairly teaches the limitation of applicant 'second oligonucleotide."

33. Applicant also asserts that another point of distinction lays in the use of a DNA polymerase to extent the second oligonucleotide. Indeed, Shuber teaches performing amplification reactions where a DNA polymerase is used. Accordingly, the recitation of a "second oligonucleotide" does not distinguish the claimed method over the prior art of record.

34. For the above reasons, and in the absence of convincing evidence to the contrary, claims 29-33, 35-38, 40, 41, 43-46, 48, and 55-57 are rejected under 35 USC 103(a).

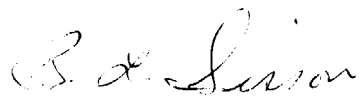
Conclusion

35. Claims 39 and 47 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

37. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

38. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
12 July 2004